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EXPERIMENTAL MEASLES IN THE MONKEY: A SUPPLEMENTAL NOTE.

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[From the Hygienic Laboratory, Washington, D. C.]

In a preliminary note¹ we briefly summarized some attempts at inoculating the rhesus monkey with blood from human cases of measles and reported some results that, we believe, demonstrate that the rhesus monkey is capable of being infected, and that when so infected may show a definite febrile reaction, resembling the course of the temperature in some types of measles in the human subject, with or without a generalized exanthem.

At this time we wish to present our work in somewhat greater detail.

Experiment 1.—Our first inoculations were made June 8, 1910. The case that furnished us with the blood for this purpose was a patient (L. F.) at the Willard Parker Hospital, New York City. The eruption in this case was reported to have appeared in the morning of June 7, 1910. Ten cubic centimeters of blood were drawn from a vein at the elbow at 1.30 p. m., June 8. It was taken to the laboratory in Washington, where, on arrival, it was found to have partly clotted, having been imperfectly defibrinated. To this blood 10 c. c. salt solution was added and the clot broken up, after which 13 c. c. of diluted blood was aspirated into a conical glass. To the remaining blood 7 c. c. more of saline solution was added and the clot further broken up, and this aspirated into a second conical glass.

At 9.30 p. m., eight hours after drawing the blood, we inoculated two rhesus monkeys; one (No. 1) received 10 c. c. intraperitoneally of the first dilution, the other (No. 2) 10 c. c. intraperitoneally of a mixture of the first and second dilutions.

A glucose-broth fermentation tube was inoculated with about 0.5 c. c. of the undiluted blood. At the end of 5 days this culture was clear, giving no visible evidence of growth.

The result of this experiment we considered negative, although in both animals there was noted a slight, but insignificant, rise in temperature on June 19, 1910, eleven days after inoculation.

An opportunity to continue our experiments did not present itself until April 25, 1911.

¹ Anderson, John F., and Goldberger, Joseph: "Experimental measles in the monkey: A preliminary note." Pub. Health Reports, vol. 26, No. 23, June 9, 1911, p. 847.

Experiment 2.—The blood used for inoculation in this experiment was from a patient (J. R. W.) at the Government Hospital for the Insane. In this case the eruption was reported to have appeared shortly after noon of April 24, 1911. A syringe of blood was drawn from a vein at the elbow at 5.15 p. m., April 25, 1911, at once defibrinated, and taken to the laboratory.

At 6.45 p. m., an hour and a half after drawing, it was used for the inoculation of two rhesus monkeys; one (No. 38) received 5 c. c. intraperitoneally, the other (No. 42) received 2.5 c. c. in the same way, but diluted with an equal volume of saline solution.

Two tubes of alkaline broth were planted with 0.5 c. c. each of the defibrinated blood. Both tubes were noted as clear, without visible evidence of growth, 5 days later.

Ten days after the inoculation (May 5) one of these animals (No. 42) showed a slight rise in temperature. Unfortunately, however, its temperature both before and after this date, was quite irregular, so that we can not be sure of its significance. In the case of the other monkey, however, the temperature rose slightly on May 5, 10 days after inoculation, went still higher on the sixth, then dropped abruptly during the night of May 6-7.

Experiment 3.—The blood used in this experiment was from a patient (I. S. E.) at the Government Hospital for the Insane.

This patient, a nurse, reported sick at 2 a. m., April 27, at which time the eruption was appearing.

Blood was drawn April 28, 1911, at 10 a. m., at once defibrinated, and taken to the laboratory.

At 12 noon, two hours after being drawn, it was employed for the inoculation of three rhesus monkeys (Nos. 7, 40, and 12). No. 7 received 5 c. c. diluted with an equal volume of salt solution subcutaneously; No. 40 received the same amount similarly diluted intraperitoneally; while No. 12 received 0.5 c. c. intracerebrally.

A glucose-broth fermentation tube was planted with about 0.5 c. c. of the defibrinated blood. At the end of 5 days this culture appeared clear, without visible evidence of growth.

The temperature of rhesus No. 7 shows a slight rise extending over May 9 and 10—that is, on the eleventh and twelfth days after inoculation; rhesus No. 40 showed a slight rise on May 6, or 8 days after inoculation; while rhesus No. 12 showed a slight rise on May 8, or 10 days after inoculation. In all three animals the elevation of temperature was too slight to be of significance in itself, nor were we disposed to attach any significance to it in any but No. 12. In this last animal, besides the slight rise in temperature on the tenth day after inoculation, we noted the presence of a few papules on the face, brows, and chin, with a rather marked diffuse erythema of the brows and lids. At the end of four days the eruption had perceptibly faded, while at the same time a fine, branny scaling was noted at the site of the fading papules.

Experiment 3a.—On May 8, at 9.45 p. m., at what we assumed would be early in a beginning reaction but which proved to be at a time when the temperature of monkey No. 12 had already receded from its slight rise, we aspirated some blood from the heart of this animal, defibrinated it, and at once injected 9 c. c. into the peritoneum of rhesus No. 44. This animal during a period of observation of 28 days gave no appreciable evidence of a reaction.

This result would appear to negative our interpretation of a reaction in monkey No. 12. This view, however, loses force when we recall that of seven monkeys that we had inoculated up to this time with blood from three cases of measles only one (No. 38, experiment 2) had shown, even in retrospect, any very significant rise in temperature. It is clear, therefore, that either the virus with which we had been working possessed a very low virulence or that the monkey is but slightly susceptible to measles. While we see no reason to doubt that the virus of measles may vary considerably in virulence, we believe from the evidence already deduced that the susceptibility of the monkey is very slight, and, judging from our later experience, we believe that this is the more important factor. In the light of these considerations we would interpret the result of this experiment as indicating a low degree of susceptibility in monkey No. 44 combined perhaps with the action of a virus of low virulence (as is in some degree probable from the ill-defined reactions in monkeys Nos. 7 and 40, inoculated with the same virus as No. 12) rather than that No. 12 had failed to react. The correctness of this view is made more probable by the result of the immunity test given No. 12 in our fourth experiment.

Experiment 4.—The blood used in this experiment was from a patient (J. R. W., 2d) at the Government Hospital for the Insane.

The eruption in this case (case 4) was reported to have appeared about 10 p. m. May 15, 1911.

Blood was drawn from a vein at the elbow at 12.15 p. m. May 16, 1911, at once defibrinated and brought to the laboratory.

At 3 p. m., three hours after it was withdrawn, this blood was used for the inoculation of rhesus monkeys Nos. 6 and 8. Rhesus No. 6 received 2.5 c. c. into the heart, while rhesus No. 8 received 0.5 c. c. into the brain and 3 c. c. into the peritoneum. At the same time we reinoculated No. 12, the monkey that in experiment 3 had given evidence of a suspicious eruption, with a view to testing his immunity and so obtaining light on the nature of his reaction.

A test of the sterility of the blood was made; as in the previous experiments a glucose-broth fermentation tube was planted with about 0.5 c. c. At the end of 5 days this culture gave no visible evidence of any growth.

The temperature curves of monkeys Nos. 6 and 8 are shown as figures 2 and 5, respectively.

In the case of rhesus No. 6 (fig. 2) there is clearly evident a sharp rise in temperature beginning May 25, nine days after inoculation. Whether this is the initial rise, or whether the slight elevation on May 22, three days preceding it, is to be regarded as such, we are unable to say, though we are inclined to believe that the latter is the case.

On May 26, 10 days after inoculation, a few irregular, scaly, coppery-tinted patches made their appearance on the chest and abdomen and it was noted that the animal had a dry, barking cough. Late in the afternoon he was bled and, unfortunately, as a result of the cardiac puncture, the animal bled to death.

By consulting figure 5 it will be seen that monkey No. 8 developed a well-marked febrile reaction 10 days after inoculation. In this case, also, we can not be sure that the rise on May 22 was not the initiation of the reaction. It seems to us almost certain that if this was not the case the rise on May 24 marks the beginning of the

reaction, for blood drawn from the heart of this animal on May 25, when its temperature was between 40.2° and 39.8° , was, as will be shown, infective by passage to another monkey. Assuming what seems to us, at least, not improbable, that the initiation of the reaction was marked by the rise on May 22, we have a fever that reached its fastigium four days later, at which time there was also noticed the first appearance of an eruption. Having reached its fastigium the temperature oscillated between 40.6° and 40.9° for three days, then dropped abruptly during the night from 40.8° to 39° .

The duration of the reaction as shown by the thermometer was therefore seven days.

Ten days after inoculation some three or four coppery papules about 3 to 4 mm. in diameter appeared on the scalp, one under the left side of the jaw, and some three patches on the abdomen. Of the latter one was about 1 cm. in diameter, not raised and slightly scaly; the other two, of which one was papular, were smaller. Within two days the eruption had extended to the limbs and back, and the lesions, pale rose-tinted maculo-papules, had greatly increased in number. On the third day after the eruption appeared, the lesions on the scalp and face were perceptibly less bright (fading), though the eruption on the abdomen appeared more abundant.

From this time on the eruption faded progressively, until on the sixth day after its appearance there were left only barely perceptible stained patches. Scaling was observed only on some of the stained areas left by the lesions on the scalp and temple.

In contrast to the beginning reaction noted in monkey No. 6 (fig. 2) and to the marked and striking reaction in monkey No. 8 (fig. 5) we have to record the absence of any evidence of reaction in monkey No. 12.

It will be recalled that this animal was first inoculated April 28 (experiment 3) and had given evidence of what we are inclined to interpret as a very mild reaction 10 days later. Although the result of an attempt at passage (experiment 3a) from this animal to No. 44 was apparently negative, the absence of any evidence of a reaction following reinoculation with blood that induced a well-marked reaction in both of two other animals (Nos. 6 and 8) inoculated at the same time, points, in our opinion, to an immunity conferred by the first inoculation evidenced by the slight reaction on May 8, already referred to.

In order to obtain further light on the nature of the reaction observed particularly in our monkeys Nos. 6 and 8, we attempted to transmit the infection by passage from these to other monkeys.

Experiment 4a.—At 11.30 a. m., May 25, we aspirated blood from the heart of rhesus No. 8. It was at once defibrinated and used for the inoculation of monkeys Nos. 20 and 22.

Rhesus No. 20 received 0.5 c. c. of the defibrinated blood intracerebrally and 3 c. c. intraperitoneally at noon. Rhesus No. 22 received a little more than 0.25 c. c. of the defibrinated blood intracerebrally and 3 c. c. intraperitoneally. About 0.5 c. c. was planted in a glucose-broth fermentation tube. At the end of 5 days the tube gave no visible evidence of growth. The temperature curves of these animals are shown in chart 2. It will be noted that in the case of rhesus No. 20 (fig. 6) the temperature began to rise May 31, six days after inoculation; the rise continued on the following day, then dropping

from its high point was continued for three days, marked by moderate oscillations and then by oscillations of greater amplitude. On June 4 we noted a suspicious mottling of the abdomen having somewhat the appearance of a pale rose-tinted macular eruption, but very poorly defined. The day after its first appearance this eruption was less clearly appreciable and on the second day after its appearance—that is, what would be the third day of eruption—it was no longer discernible.

We are inclined to interpret this slight and poorly defined rise in temperature followed by a suspicion of an eruption as indicative of a reaction in this animal.

In the case of rhesus No. 22 (fig. 7) we have a very clearly defined reaction. As in monkey No. 20, we noted a beginning rise on May 31, six days after inoculation, although we think it probable that the initial rise was on May 30. The temperature continues its upward course for three days, reaching its fastigium on June 3, followed by an abrupt drop the next morning. On the day when the temperature reached its fastigium a few suspicious maculo-papules were observed on the abdomen and chest and at the same time some scaly, coppery, irregular confluent patches were observed on the right cheek.

The day following its appearance the coppery patches on the cheek were much faded, while the maculo-papules on the abdomen remained unchanged. Two days after the appearance of the eruption it had faded to such a degree that it could no longer be definitely distinguished.

Experiment 4b.—At 3.30 p. m., May 26, 1911, we aspirated blood from the heart of rhesus No. 6, at once defibrinated, and used it for the inoculation of monkeys Nos. 35 and 37.

Rhesus No. 35 received at 4 p. m. 2 c. c. subcutaneously and 2 c. c. intravenously. At 4.30 p. m. rhesus No. 37 received 2 c. c. of the defibrinated blood intravenously. About 0.5 c. c. of the defibrinated blood were planted in a glucose-broth fermentation tube. No visible evidence of growth was discernible at the end of 5 days' incubation at 37°.

The temperature curves of monkeys Nos. 35 and 37 are given on chart 1 (figs. 3 and 4). It may be seen that in the case of monkey No. 35 (fig. 3) the temperature began to rise, possibly on the fifth, and certainly on the sixth, day after inoculation, and continued its upward course on the following day, when it attained its fastigium. It remained high one day, then began to decline. The decline extended over a period of three days. The total duration of the fever was six or seven days, depending on what one considers the initial rise.

On the day when the decline in the fever began—that is, nine days after inoculation—there was observed a diffuse erythema about the orbits, with the appearance of small purplish-red papules on the left upper lid. There were, besides this, two or three maculo-papules on the face. On the abdomen there appeared a sparse eruption of pale coppery or rose-tinted macules. The day following their appearance the papules on the lid were gone and the periorbital erythema appeared less bright. The macules on abdomen were clearly discernible and appeared to have extended to the thighs. Three days after its appearance the eruption was much less evident and in another day or two was altogether indistinguishable.

In the case of rhesus No. 37 (fig. 4) a febrile reaction is clearly evident, lasting seven days. The initial rise took place five days after inoculation. The temperature dropped the following day, but rose again, reaching its highest point seven days after inoculation. Six days after the initial rise the temperature dropped rapidly, falling within 24 hours to a point slightly below its normal level. An eruption could not be detected in this animal.

Summarizing the results of experiments 4, 4a, and 4b, we have, first, a clearly defined temperature reaction in both of two animals (Nos. 6 and 8), with the appearance of a generalized maculo-papular eruption in one of them, following inoculation with defibrinated blood from case 4, which in culture appeared to be sterile; second, a well-developed temperature reaction in at least three (Nos. 22, 35, and 37) of four monkeys, with the appearance of sparse eruptions in two of these as well as in the fourth (No. 20), in which the temperature reaction was not clearly defined, following inoculation with defibrinated blood from the first pair of animals (Nos. 6 and 8), that was also apparently sterile in culture.

The only reasonable interpretation of this series of events is that monkeys Nos. 6 and 8 were infected with measles from a human case and that the infection was transmitted by passage from these to four other monkeys (Nos. 20, 22, 35, and 37). We may add in this connection that we have succeeded in propagating the infection by a second passage from rhesus No. 35 to rhesus No. 81 through three monkey generations. We reserve the details of this, however, for a later report.

SUMMARY.

We have inoculated nine rhesus monkeys with defibrinated blood from four cases of measles.

The blood was drawn from the general circulation in case 1 (experiment 1) at the end of not less than 30 hours, in case 2 (experiment 2) at the end of not less than 24 to 28 hours, in case 3 (experiment 3) at the end of not less than 32 hours, and in case 4 (experiment 4) at the end of not less than 14 hours after the appearance of the eruption.

In this connection it may be well to recall that Hektoen (1905) has shown by inoculations in man that the virus is present at least during the first 30 hours of the eruption.

In broth culture the blood in all four cases appeared to be sterile.

The inoculations were intraperitoneal in experiments 1 and 2; subcutaneous, intraperitoneal, and intracerebral in experiment 3; and intracardiac and combined intracerebral and intraperitoneal in experiment 4.

Of the nine animals inoculated with human blood, only four (Nos. 38, 12, 6, and 8) gave any very significant evidence of a reaction.

Varying quantities of blood were used in the inoculations with human measles blood. The two clearly marked reactions followed the injection of 2.5 c. c. in one animal (No. 6) and 3.5 c. c. in the other (No. 8).

We have made passage inoculations in five rhesus monkeys with defibrinated blood from monkeys that had given evidence of a reaction following an inoculation with measles blood.

The blood in all three instances was drawn direct from the heart, and without exception appeared to be sterile in broth culture at 37°.

The passage inoculations were intraperitoneal (rhesus No. 44) in experiment 3*a*, combined intracerebral and intraperitoneal (rhesus Nos. 20 and 22) in experiment 4*a*, and intravenous (rhesus No. 35) and combined subcutaneous and intravenous (rhesus No. 37) in experiment 4*b*.

Of the five animals inoculated by passage, one (No. 44) gave apparently no reaction, one (No. 22) gave an ill-defined reaction, and three (Nos. 20, 35, and 37) gave well-marked reactions.

The inoculations in the animals that gave well-marked reactions were with blood varying in amount from 2.25 to 4 c. c.

Of two animals (Nos. 20 and 22) receiving nearly equal amounts of the same blood by the same method of inoculation, the one (No. 22) receiving the slightly smaller amount gave the better, more clearly defined reaction. On the other hand, in the case of two other animals (Nos. 35 and 37) the one receiving the larger amount of blood (No. 35) exhibited the sharper reaction.

In the five animals (Nos. 6, 8, 22, 35, and 37) in which the reaction is clearly defined the period of incubation—that is, the time elapsing between inoculation and beginning reaction—was six days in two (Nos. 6 and 8) and five days in three (Nos. 22, 35, and 37).

This period probably varies considerably, for in another experiment (second passage or third monkey generation, rhesus 35 to rhesus 81), the details of which we reserve for a later report, the interval was seven days.

CONCLUSIONS.

The rhesus monkey is capable of being inoculated with measles with blood from a human case.

This susceptibility appears at best not to be very great and is subject to considerable individual variation.

The virus of measles gives no visible growth in standard glucose broth in a fermentation tube.

We again wish to express our thanks to Dr. William A. White, superintendent of the Government Hospital for the Insane, and his associates, to Dr. J. D. Morgan and to Dr. Robert J. Wilson for access to cases of measles.

CHART 1.

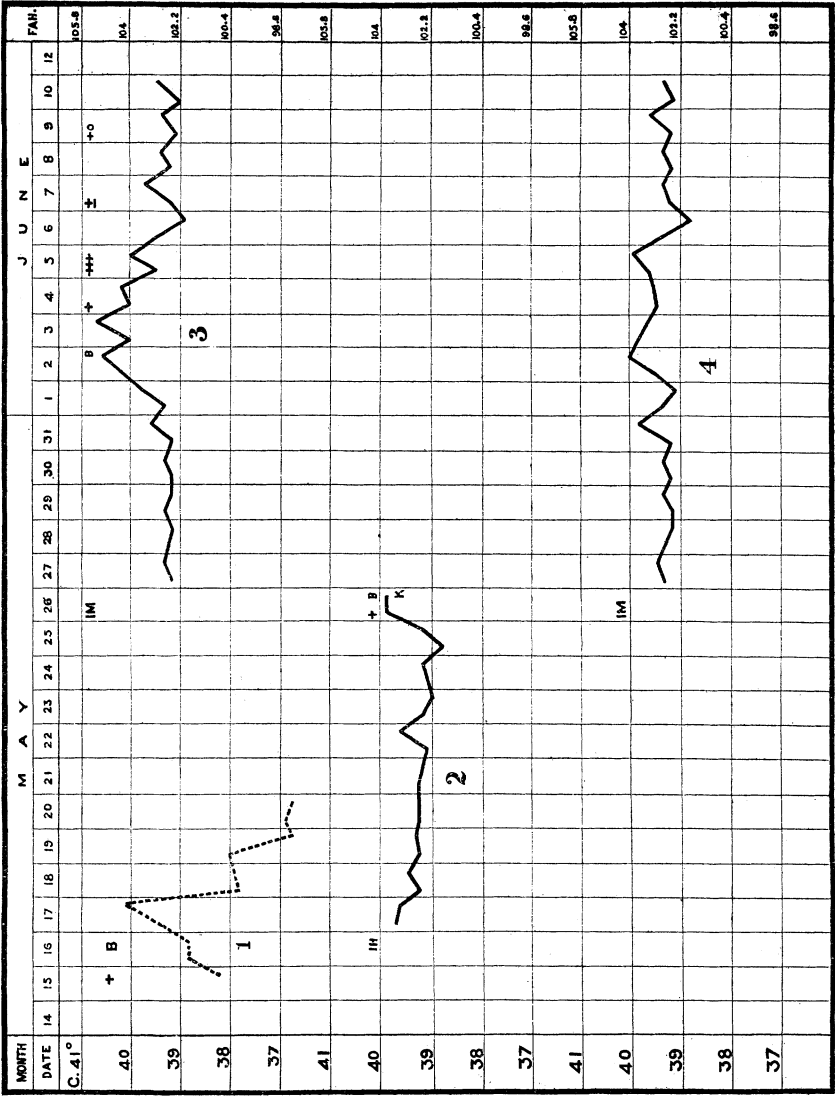


FIG. 1. Temperature curve of case 4, the source of the virus used for inoculation of rhesus Nos. 6 and 8 (figs. 2 and 5).
2. Temperature curve of rhesus No. 6, inoculated with 2.5 c. c. defibrinated blood of case 4 (fig. 1) into heart.
3. Temperature curve of rhesus No. 35, inoculated with defibrinated blood of rhesus No. 6.
4. Temperature curve of rhesus No. 37, inoculated with defibrinated blood of rhesus No. 6.

CHART 2.

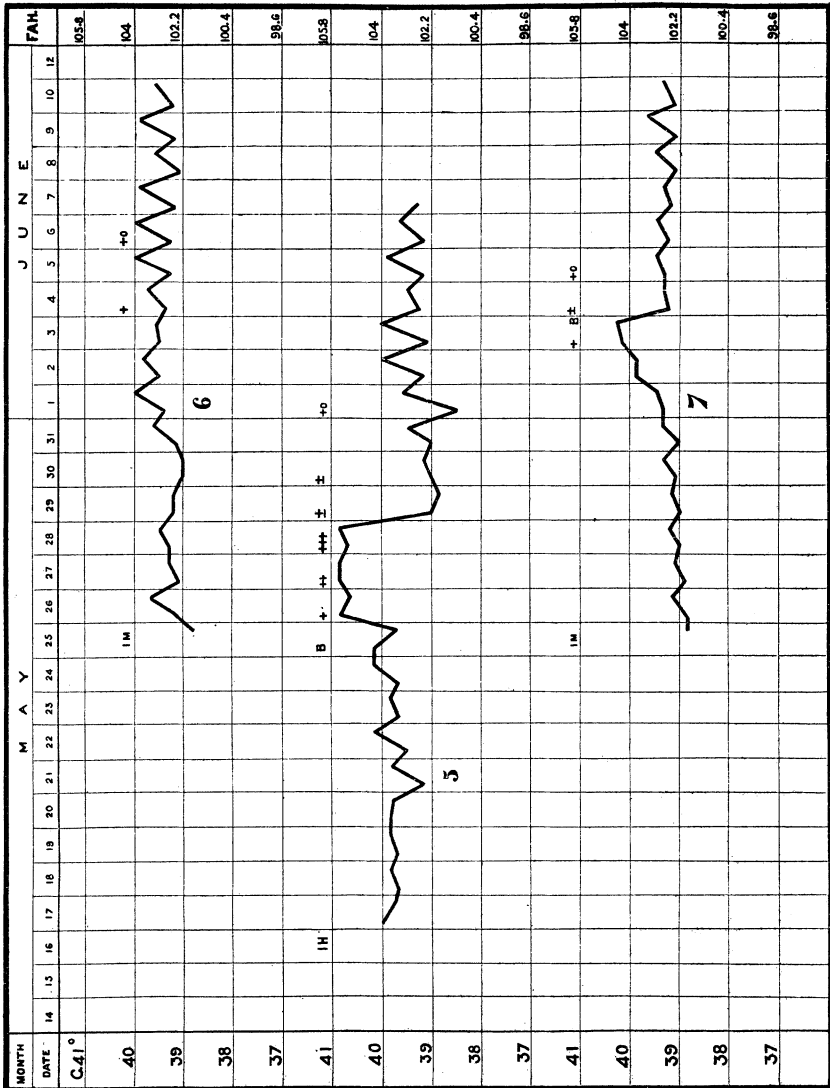


Fig. 5. Temperature curve of rhesus No. 8, inoculated in brain with 0.5 c. c. and into peritoneum with 3 c. c. defibrinated blood of case 4 (fig. 1).
 6. Temperature curve of rhesus No. 20, inoculated with defibrinated blood of rhesus No. 8.
 7. Temperature curve of rhesus No. 22, inoculated with defibrinated blood of rhesus No. 8.